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10/550,436

09/23/2005

Masuo Obinata

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WENDEROTH, LIND & PONACK, L.L.P.

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EXAMINER

SINGH, ANOOP KUMAR

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/550,436	Applicant(s) OBINATA ET AL.	
	Examiner ANOOP SINGH	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 November 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-26 is/are pending in the application.
- 4a) Of the above claim(s) 1-12 and 24-26 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 13-23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>9/23/2005</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

Applicants' election of claims 13-23 (Group IV) in the reply filed on November 19, 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Applicants have also elected BMP-2 and OSM as a single species of a combination of two or more cytokine.

Claims 1-12 and 24-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 11/19/2007.

Claims 13-23 are under current examination.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 13-19, 21 and 22 are rejected under 35 U.S.C. 101 because the claimed invention is directed to a product of nature. The claims are directed to 'a set of cytokines to regulate the differentiation of cells of mammal which comprises a combination of cytokines that is capable of determining three or more direction of differentiation of the multipotent stem cell". As recited, instant claims read on a set of cytokine that regulates the differentiation of cells of mammal *in vivo*. It is generally known in prior art that a complex set of cytokines cascade play an important role in cell differentiation in vivo. In the instant claims, claim s embrace a set of cytokine that regulates the differentiation of cells *in vivo* without cytokine

or cells ever being isolated. Therefore, broadly interpreted, a set of cytokine that regulate differentiation of cells would read on differentiation of non-isolated cells in presence of naturally secreted cytokines *in vivo*. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty*, 447 U.S. 303, 206, USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, *e.g.*, by the insertion of the term, “isolated” or “differentiation of bone stromal cell under *in vitro* condition” as taught by the specification. See also, MPEP § 2105.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 13-22 rejected under 35 U.S.C. 102 (b) as being anticipated by de Hooge et al (American Journal of Pathology, 2002, 1733-1743).

Applicant cannot rely upon the foreign priority papers of Japanese application no. 2003-83106 and 2003-95242 to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15. A certified English translation of the foreign priority document would remove the availability of the instant reference under 102(b) if all the claimed subject matter were in fact disclosed in the foreign priority document. It

is noted that instant claims would be rejected under 35 U.S.C. 102 (a) once foreign priority document has been perfected.

Claims are directed to a set of cytokine to regulate differentiation of cells of mammal comprising a combination of two or more cytokines as an effective ingredient.

De Hooge et al teach a set of cytokine that regulates the differentiation of mammalian cell under *in vitro* condition. Specifically, de Hooge et al disclose C2Cl2 a murine pluripotent cell in presence of different combination of cytokine including oncostatin M (OSM) and BMP-2 (see page 1735, col. 2, para. 1). de Hooge et al also teaches that addition of OSM to a BMP-2 concentration enhances the effect of BMP-2 induces ALP activity indicating more osteoblast like nature of the cells (see page 1736, col. 2, para. 3 and figure 5A). It is noted that the claims recite an intended use for the cytokines, to regulate differentiation of cells. Intended used does not impart patentable weight to a product. See MPEP 2111.03:

Intended use recitations and other types of functional language cannot be entirely disregarded. However, in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. In re Casey 370 F.2d 576, 152 USPQ 235 (CCPA 1967); In re Otto, 312 F.2d 937, 938, 136 USPQ 458, 459, (CCPA 1963).

Additionally, it is noted that limitation of cell differentiation to a specific lineage or degree of differentiation to a specific lineage or its potential use in *in vivo* research or screening method would be inherent as one of ordinary skill in the art would have used this set of cytokine to regulate differentiation of cells. Where, in the instant case, the claimed and prior art products are identical or substantially

identical, or are produced by identical or substantially identical processes, “[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency’ under 35 U.S.C. 102, on prima facie obviousness’ under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted].” The burden of proof is similar to that required with respect to product-by-process claims. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).

Additionally, “Products of identical chemical composition can not have mutually exclusive properties.” A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Accordingly, de Hooge anticipates claims 13-22.

Claims 13-22 rejected under 35 U.S.C. 102 (e) as being anticipated by West et al (US Patent application no. 2003/0224345, dated 12/4/2003, filing date 6/22/2002, effective filing date 6/24/2001).

West et al disclose a set of cytokines that are capable of directing differentiation of pluripotent and multipotent stem cells. It is noted that West et al contemplate simultaneously or sequentially exposing the totipotent or pluripotent cell with differentiation inducing compounds including a set of cytokine including OSM and BMP-2 (See abstract and claims 21, 24 and 25). Additionally, West et al also teach that differentiation inducing agent may be used in any appropriate totipotent or pluripotent stem cells, and cells therefrom including mesenchymal stem cells, hematopoietic stem cells and marrow stromal stem cells meeting the limitation of claim 13 and 14 (see para. 69 of the published application). The teaching of West et al also include pluripotent cells that is capable of differentiating

into mesenchymal stem cells that can differentiate into bone, cartilage and muscle; hemotopoietic stem cells that can differentiate into blood, endothelium, and myocardium; neuronal stem cells that can differentiate into neurons and glia in presence of combination of growth factors and cytokine, which is compared with a references panel of differentiated or partially differentiated cells including heart, vascular, skeletal and smooth muscle cells in order to establish the differentiation of pluripotent cells meeting the limitation of claims 15 and 19 (see para. 16 and claim 24). Furthermore, West et al also teach compositions of cytokines including OSM and BMP-2, and/or other differentiation-inducing agents, alone or in combination that are identified and used to direct the development of characterized cell populations in treatments or transplantation therapies thereby meeting the limitation of claim 21 and 22. The set of cytokine disclosed by West et al is structurally and functionally similar to one claimed in the in the instantly claimed composition. Where, in the instant case, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, “[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency’ under 35 U.S.C. 102, on prima facie obviousness’ under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted].” The burden of proof is similar to that required with respect to product-by-process claims. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).

Additionally, “Products of identical chemical composition can not have mutually exclusive properties.” A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Accordingly, West anticipates claims 13--22.

Claims 13-22 rejected under 35 U.S.C. 102 (b) as being anticipated by Taichman et al (US Patent 5733541, dated 3/21/1998).

Claims are directed to a set of cytokine to regulate differentiation of cells of mammal comprising a combination of two or more cytokines as an effective ingredient. It is noted that the claims recite an intended use for the cytokines, to regulate differentiation of cells. Intended used does not impart patentable weight to a product.

Taichman et al disclose a set of cytokine that osteoblasts produce which stimulate the propagation of hematopoietic cells and provides a microenvironment that promotes the propagation of hematopoietic cell including OSm and BMP-2 (see table 3. col. 12). MPEP 2111.03: Intended use recitations and other types of functional language cannot be entirely disregarded. However, in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. In re Casey 370 F.2d 576, 152 USPQ 235 (CCPA 1967); In re Otto, 312 F.2d 937, 938, 136 USPQ 458, 459, (CCPA 1963). In the instant case, set of cytokines disclosed by Taichman et al is structurally similar and therefore would capable of performing the intended use. Accordingly, Taichman et al anticipates claims 13-22.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 13 -23 are rejected under 35 U.S.C. 103(a) as being unpatentable over West et al (US Patent application no. 2003/0224345, dated 12/4/2003, filing date 6/226/2002, effective filing date 6/24/2001), Okuyama (Exp Cell Res. 1995; 218(2):424-9, IDS) and Yanai et al (In Vitro Cell Dev Biol Anim. 2001; 37(10):698-704, IDS).

Instant rejection is applied using the references of West to include bone marrow stromal cell that has been derived from temperature sensitive SV-40 T-antigen gene transgenic mice.

West et al disclose a set of cytokines that are capable of directing differentiation of pluripotent and multipotent stem cells. It is noted that West et al contemplate simultaneously or sequentially exposing the totipotent or pluripotent cell with differentiation inducing compounds including a set of cytokine including OSM and BMP-2 (See abstract and claims 21, 24 and 25). Additionally, West et al also teach that differentiation inducing agent may be used in any appropriate totipotent or pluripotent stem cells, and cells therefrom including mesenchymal stem cells, hematopoietic stem cells and marrow stromal stem cells meeting the limitation of claim 13 and 14 (see para. 69 of the published application). The teaching of West et al also include pluripotent cells that is capable of differentiating into mesenchymal stem cells that can differentiate into bone, cartilage and muscle; hemotopoietic stem cells that can differentiate into blood, endothelium, and myocardium; neuronal stem cells that can differentiate into neurons and glia in presence of combination of growth factors and cytokine, which is compared with a references panel of differentiated or partially differentiated cells including heart, vascular, skeletal and smooth muscle cells in order to establish the differentiation

of pluripotent cells meeting the limitation of claims 15 and 19 (see para. 16 and claim 24). Furthermore, West et al also teach compositions of cytokines including OSM and BMP-2, and/or other differentiation-inducing agents, alone or in combination that are identified and used to direct the development of characterized cell populations in treatments or transplantation therapies thereby meeting the limitation of claim 21 and 22. Further West et al also teach using set of cytokine that is used for in vitro differentiation of bone marrow stromal cell for the screening of other candidate agent that are capable of differentiating cells. The set of cytokine disclosed by West et al is structurally and functionally similar to one claimed in the in the instantly claimed composition. Where, in the instant case, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, “[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency’ under 35 U.S.C. 102, on prima facie obviousness’ under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted].” The burden of proof is similar to that required with respect to product-by-process claims. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).

Although, West et al teach a set of cytokine capable of regulating the differentiation of cells of mammal, but differed from claimed invention by not disclosing bone marrow stromal cell that has been derived from temperature sensitive SV40 T antigen gene transgenic mice.

Okuyama teach stromal cell from bone marrow of temperature sensitive T-antigen transgenic mouse that could be induced to cell type of mesenchymal lineages (see page 424, material and method section) and have potential to differentiate towards muscle cell, endothelial cell, osteogenic and adipocytes. Although, Okuyama contemplated studying differentiation potential of these cells at

different developmental stage (see page 428, col. 2, last para.), but differed from claimed invention by not disclosing exposing cells with OSM and BMP-2.

Yanai et al teach bone marrow stromal cell line (TBR) derived from temperature sensitive T-antigen transgenic mouse that could be induced to differentiate into myogenic, osteogenic, and adipogenic differentiation (abstract). Yanai et al disclose that marrow stromal cell create the hematopoietic microenvironment in which maintenance and differentiation of the hematopoietic stem cells are regulated, and regulation of mesenchymal cell differentiation of stromal cells may be crucial in maintaining the hematopoietic microenvironment in bone marrow. Yanai et al cite other references to indicate that LIF, bone morphogenetic protein-2 (BMP-2), and OSM are known to be regulatory factor for mesenchymal cells (see page 702, col. 1, para. 2). Although, Yanai et al studies the effect of OSM on mesenchymal cell differentiation of marrow stromal cell resulting in differentiation of these cells into skeletal muscle, whereas differentiation of TBR10-1 cells into smooth muscle was inhibited by the treatment of OSM, but differed from claimed invention by not exposing OSM in combination of other differentiation inducing cytokine.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the set of cytokines to include BMP-2 and OSM in the medium disclosed by West in the bone stromal cells that have been derived from temperature sensitive SV-40 T -antigen gene transgenic mouse. West taught that set of cytokine could be exposed simultaneously or sequentially to evaluate differentiation of the cells, therefore one would be motivated to use and test the various cytokine and differentiation inducing factors for their specific affects on the differentiation of bone marrow stromal cell cells , while Okuyama provided guidance with respect to stromal cell that could be induced to cell type of mesenchymal lineages (see page 424, material and method section) that have potential to differentiate towards muscle cell, endothelial cell, osteogenic and

adipocytes. Yanai et al cited other references to indicate that LIF, bone morphogenetic protein-2 (BMP-2), and OSM were known to be regulatory factor for mesenchymal cells. One of skill in the art would have been studied these references and motivated to provide a set of cytokine capable of regulating the differentiation of cells optimized to differentiate cells of multiple lineage including smooth muscle, cardiomyocyte and endothelial cells. One who would practiced the invention would have had reasonable expectation of success because West had already described a method to evaluate differentiation inducing agent including OSM and BMP by methods known to a cell culturist in cells disclosed by Okuyama and Yanai et al. Given that agent such as LIF, oncostatin M and BMP-2 were available for use to culture bone marrow stromal cells as per the teachings West and Yanai et al it would have obvious for to one of ordinary skill in the art to optimize the culture medium for optimal regulation of differentiation of the cells in multiple directions including differentiation towards skeletal, muscle, cardiomyocyte or endothelial cells as disclosed in the instant application.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Lanza et al (US Patent application 2003/0027330, dated 2/6/2003, effective filing date 4/2/2001).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anoop Singh
AU 1632

/Thaian N. Ton/
Primary Examiner, Art Unit 1632